State of Art

Health Effects and Sources of Indoor Air Pollution. Part II[1-3]

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Health Effects of Indoor Air Pollution (Cont'd)

Biological Agents

Introduction. Numerous and diverse biological agents that cause human disease are present in indoor air. Mechanisms of disease pathogenesis are now well understood for many of these agents; they produce illness primarily through infection of the respiratory tract and through immune responses. Because of the diversity of these agents and their associated illnesses, this review will address only selected and illustrative examples of the health effects of biological agents in indoor air. More detailed treatments are included in the National Research Council's report on indoor air (15) and in other recent publications (19-24). With regard to immunologically mediated diseases, we review hypersensitivity pneumonitis and humidifier fever and the role of selected biological agents in the etiology and exacerbation of asthma. We will also briefly consider 2 problems of infection associated with indoor air: the transmission of Legionnaires' disease and infection with *Aspergillus* through contamination of hospital and office environments.

Exposure to Biological Agents. Myriad biological agents may contaminate the air within a home, office, or other indoor environment. The most prevalent are viruses, bacteria, actinomycetes, fungal spores, algae, amoebae, arthropod fragments and droppings, and animal and human dander (244, 245). In homes and in other environments, moisture is critical for the growth of microorganisms. Humidifiers, air conditioning systems, and areas of water damage may provide a suitable environment for proliferation of microorganisms. The initial colonization may be from outdoor or indoor sources or from organisms in the water.

Most bacteria in indoor air originate from humans, whereas most fungi in indoor air originate from spores from outdoor sources (15, 245). Many indoor environments provide sufficient moisture and an appropriate temperature for the growth of fungi, bacteria, mites, and other biological agents. Moist surfaces of leather, wood, and plaster, soaps, greases and some oils, cloth fabrics, paper, and some pastes and glues can support growth of microorganisms, as can wicker baskets and chairs, and ornamental plants. Moist locations within a home include bathrooms, damp or periodically flooded basements, and areas with water leaks. The evaporation pans of refrigerators, shower heads, and hot tubs have also been identified as possible sources of bacteria (245).

Concentrations of microorganisms in the indoor environment have not been well-characterized. Standardized sampling methods have not been developed,

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and collection efficiency for biological particles would be expected to vary with particle size and density and with the aerodynamics of the sampling method. Further variation in concentration will arise from cycles of proliferation and of the physical forces that place organisms into the air. Thus, reports on concentrations as numbers of colony-forming units (cfu) per cubic meter cannot be interpreted without knowledge of the specific species, the efficiency of collection by the sampling apparatus, and the conditions under which sampling was performed.

Hypersensitivity Pneumonitis and Humidifier Fever. In 1970, Banaszak and coworkers (246) reported that 4 of 27 workers in one office had developed hypersensitivity pneumonitis from exposure to thermophilic actinomycetes contaminating an air-conditioning system. Subsequently, hypersensitivity pneumonitis and humidifier fever, an influenza-like syndrome without prominent pulmonary manifestations, have been described in association with contaminated air treatment systems in offices, homes, and automobiles (247–249).

A wide range of biological sources for potentially sensitizing antigens has been described, including thermophilic actinomycetes, diverse fungi, bacteria, amoebae, and nematodes. In some outbreaks, a specific antigenic exposure underlying the illness could not be identified (250–253). The offending antigens have been introduced into indoor environments through central and room humidifiers (252, 254–257), contaminated heating and cooling systems (246, 251, 258, 259), moisture-damaged building materials (260), cool mist vaporizers used in the home (250), and automobile air conditioning systems (261).

The literature on hypersensitivity pneumonitis and humidifier fever consists primarily of individual case reports and small series from identified outbreaks. While these studies do not address the overall prevalence and incidence of these illnesses, they do provide comprehensive clinical descriptions. As with hypersensitivity pneumonitis, associated with other exposures, both acute and chronic forms may result from exposure to indoor antigens (252). Persons with the acute form characteristically have fever, chills, cough, and dyspnea after exposure. In the more chronic form, patients may present with progressive dyspnea and lung function impairment. The diagnosis of either form is based on the clinical history, evidence of exposure, the presence of precipitating antibodies to environmental antigens, response to inhalation challenge, and improvement with cessation of exposure. Precipitating antibodies may be present in exposed but unaffected persons, however.

Asthma. Both outdoor and indoor air pollutants have long been considered as important in the etiology and exacerbation of asthma. In a home, components of house dust, animal proteins, and fungal spores may provoke asthma through immediate hypersensitivity (262–264). In an office, aeroallergens and irritant agents may be present. Pollens and molds from outdoor sources may penetrate into the home, office, and other environments.

While qualitative and quantitative aspects of aeroallergens in indoor air have been well described, their contribution to asthma has been more difficult to characterize. Epidemiologic studies have been conducted to examine the relationship between the severity of asthma and exposure to aeroallergens and other indoor pollutants (for example, see 198, 199). However, the results of these studies are limited by the difficulties of monitoring personal exposures to pollutants and of separating the effects of the many factors that influence asthma's severity. A detailed presentation of these studies is beyond the scope of the present review. Comprehensive discussions of the aeroallergens in indoor air can be found in the National Research Council's report on indoor pollutants (15) and in recent reviews by Reed and coworkers (263) and Ausdenmoore and Fischer (264).

We briefly consider the data on house dust mites and asthma because this antigen has been intensively investigated and the literature is illustrative. House dust mites live in mattresses and furniture stuffing, and their numbers tend to increase with the environment's humidity (264, 265). The mite, *Dermatophagoides pteronyssinus*, has been shown to be highly prevalent in homes in Europe, and this species as well as *Dermatophagoides farinae* have been found in houses in the United States (266–268). The major allergen of *D. pteronyssinus* has been designated as antigen P_1. This potent allergen may be found in high concentrations in dust from beds and floors; airborne levels in homes with undisturbed dust are quite low but increase with domestic activity (269, 270).

Clinical studies provide convincing evidence that inhalation of house dust contaminated with mites causes asthma (271). However, the prevalence of house-dust-mite-related asthma has not been established through appropriate population-based studies. Increased exposure has been associated with a greater risk of asthma in adults (272). Preventive measures, including frequent cleaning, removal of carpeting, pillows, and quilts with feathers, and covering mattresses with plastic reduce the concentrations of mites in house dust (271, 273). Some clinical trials suggest benefits from these measures in children and adults, although the studies are not uniformly positive (274–279).

Legionnaires' Disease. Legionnaires' disease refers to acute bacterial infection with *Legionella pneumophila.* The clinical features and many aspects of the epidemiology of Legionnaires' disease have been well characterized (280). Both epidemic and sporadic cases may result from contamination of indoor air with *Legionella pneumophila.* Because Legionnaires' disease exemplifies the spread of an infectious illness by air treatment systems, we will consider representative outbreaks.

Legionella pneumophila has been isolated from water sampled from cooling towers and evaporative condensers, devices used to cool water for buildings (281). Failure to treat the water with appropriate disinfectants may permit the growth of microbial agents, including the Legionnaires' disease bacterium. Outbreaks of Legionnaires' disease have been described in association with contaminated air treatment equipment in hospitals and offices. The 1976 epidemic in Philadelphia has been attributed to airborne transmission of the bacterium, although its source has never been identified (282). More convincing evidence of airborne transmission has been obtained from other outbreaks, however. Dondero and coworkers (283) described a 2-month-long outbreak in those in contact with a single hospital as patients, visitors, employees, or passersby. *Legionella pneumophila* was present in water in an auxiliary cooling tower in use during this time; the aerosol that drifted away from the tower entered the hospital's ventilation system and also dropped into the street below.

In an outbreak in a new sealed office building in San Francisco, at least 14 of 1,000 workers developed Legionnaires' disease over a 2-wk period (284). *Legionella pneumophila* was grown from water samples taken from the building's air-conditioning cooling tower, and further cases were not observed after the

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cooling tower was disinfected. Airborne spread of the bacterium within single buildings has probably led to other outbreaks as well (285–288).

Nosocomial cases of Legionnaires' disease have also been attributed to aerosols generated by respiratory therapy devices (289). Hospital water supplies may become contaminated with *Legionella pneumophila* (290, 291), and the organism has been cultured from plumbing fixtures, such as shower heads (292–294). The mechanism by which pneumonia is acquired from these waterborne organisms has not been identified, but aerosolization and contamination of indoor air seem plausible.

Aspergillus *Infections.* Nosocomial infections with *Aspergillus* species also illustrate the potential for disease transmission through ventilation systems. Patients with defects of cell-mediated immunity are particularly vulnerable to infection by these organisms. Outbreaks of *Aspergillus* infection have been described in hospitalized patients in association with airborne spread related to inadequate ventilation systems (295), contaminated ventilation systems (296, 297), improperly functioning ventilation systems (298), construction activity (299), and building materials (300).

Formaldehyde

Introduction. The recent recognition of numerous sources of formaldehyde in indoor environments has raised widespread concern about the health hazards of this pollutant. A colorless volatile gas with a characteristic odor, formaldehyde is highly soluble in water and thus irritating to the mucous membranes of the eyes and upper respiratory tract. The public first became aware of possible health effects of formaldehyde through reports that residents of homes insulated with urea formaldehyde foam insulation (UFFI) experienced a wide variety of symptoms that were attributed to release of formaldehyde from this material. Although use of UFFI has virtually ceased in the United States and Canada, concern remains about the health effects of formaldehyde because of its widespread use in industrial processes, building materials, and consumer products. The 1981 report of the Committee on Aldehydes of the National Research Council (301) and the 1983 report of the Consensus Workshop on Formaldehyde (302) provide recent assessments of formaldehyde's toxicity, and L'Abbe and Hoey (303) have reviewed the health effects of UFFI.

Exposure. Formaldehyde has many sources in the home: paper products, floor coverings, carpet backings, adhesive binders, permanent-press clothing, tobacco smoking, combustion processes, resins, and cosmetics. Particularly high concentrations may result from the use of UFFI, a resin of urea, formaldehyde, and water. UFFI can be used to insulate already constructed homes and as many as 200,000 homes in the United States may have been insulated with this material in 1980 (15). After installation UFFI releases formaldehyde for a short time as it hardens. If the UFFI is improperly cured, release of formaldehyde may be sustained and may take place in large quantities.

Godish (304) monitored for formaldehyde in residences with and without UFFI. Concentrations in the homes with UFFI ranged from 0.02 to 0.13 ppm, whereas in the homes without UFFI they ranged from 0.03 to 0.07 ppm. Georghiou and coworkers (305) measured formaldehyde in 44 homes with UFFI and in 6 control homes. The homes with UFFI more recently installed tended to have higher concentrations. Eighty-four percent of the repeated measurements in such homes exceeded 0.06 ppm. In homes with UFFI installed more than 3 yr prior to monitoring, only 22% of the formaldehyde concentrations exceeded 0.06 ppm, whereas in homes with UFFI installed more recently, 58% of the samples exceeded 0.1 ppm.

Mobile homes are constructed with large quantities of particle board, which is manufactured with formaldehyde-containing adhesive binders. As a result of this construction method, formaldehyde concentrations tend to be higher in mobile homes than in conventional homes. In several studies, formaldehyde levels have been surveyed in mobile homes and have been found to greatly exceed those found in conventional homes. In a survey of mobile homes in Texas, Stock and coworkers (306) reported integrated concentrations ranging from less than 0.02 to 0.78 ppm. Dally and colleagues (307) studied mobile homes whose residents were concerned about formaldehyde exposure and found that 50% of the values were greater than 0.47 ppm and that the range was as high as 3.6 ppm.

Numerous potential sources of formaldehyde exist in office buildings, including insulation, new furniture and furnishings, carpets, carbonless copy paper, and cigarette smoke. Formaldehyde has been measured infrequently in office buildings, and then usually as part of an evaluation of building-related illness. Breysse (308), summarizing data from 20 health hazard evaluations conducted in Washington, reported that concentrations ranged from 0.01 to 0.30 ppm. While formaldehyde has been implicated as the causative agent in about 4% of episodes of building-related illness investigated by the National Institute of Occupational Safety and Health (309), concentrations in these episodes have been well below the permissible exposure level established by the Occupational Safety and Health Administration.

Health Effects. Both acute and chronic health effects have been associated with formaldehyde exposure. A variety of short-term signs and symptoms are commonly accepted as causally related to exposure; some occur at levels that have been measured in residential air (table 9). The wide range of concentrations at which individual symptoms occur suggests a large variation in individual sensitivity to formaldehyde. As would be an-

TABLE 9

ACUTE HUMAN HEALTH EFFECTS OF FORMALDEHYDE AT VARIOUS CONCENTRATIONS*

Reported Effects	Formaldehyde Concentration (ppm)
None reported	0.0–0.5
Neurophysiologic effects†	0.05–1.5
Odor threshold	0.05–1.0
Eye irritation‡	0.01–2.0
Upper airway irritation	0.10–25
Lower airway and pulmonary effects	5–30
Pulmonary edema, inflammation, pneumonia	50–100
Death	> 100

* Adapted from table 7-2 in reference 301.
† As measured by determination of optical chronaxy, electroencephalography, and sensitivity of dark-adapted eyes to light.
‡ The low concentration (0.01 ppm) was observed in the presence of other pollutants that may have been acting synergistically

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TABLE 10

SURVEYS OF OCCUPANTS LIVING OR WORKING IN MOBILE HOMES OR HOMES WITH UFFI

Study Population	Findings (%)	Comments
424 adults, 99 children living in 334 mobile homes. Complaint investigations,* Washington State (310)	Eye irritation: A, 58; C, 41 Throat irritation: A, 66; C, 62 Chronic headache: A, 40; C, 16 Chronic cough: A, 9; C, 33 Memory lapse/drowsiness: A, 24; C, 7	Formaldehyde levels: 0.03 to 1.77 ppm; no control group; exposure-response not examined
256 adults and children living in 65 mobile homes or 35 other structures. Complaint investigations,* Wisconsin (307)	Eye irriation: 68 Throat irritation: 57 Headache: 53 Cough: 51 Difficulty sleeping: 38 Wheezing: 20	Formaldehyde levels: 0.0 to 3.68 ppm; no control group; exposure-response not examined
162 residents of 68 homes with UFFI. Complaint investigations,* Connecticut (311)	Eye irritation: 39 Nose/throat/lung irritation: 48 Headache: 17 No apparent relationship between symptoms and crude formaldehyde level	Formaldehyde levels: 0.0 to 10 µg/L, with detectable and nondetectable levels
Unknown number of residents in 443 families living in mobile homes. Complaint investigations,* Texas (312)	No difference in symptom prevalence in families living in homes with and without detectable levels	Formaldehyde levels: 0.0 to 8 ppm; comparison of homes with detectable and nondetectable levels
1,396 residents of UFFI homes; 1,395 residents of non-UFFI homes. Retrospective cohort, New Jersey (313)	Exposed more likely to report wheezing than nonexposed: Wheezing: Exposed, 0.6 Nonexposed, 0.1 Burning skin: Exposed, 0.7 Nonexposed, 0.1 Subgroup in whose homes odor persisted > 7 days after foam installed, had higher symptom incidence	Population-based study: formaldehyde concentrations not measured
70 exposed employees of 7 mobile home care centers; 34 nonexposed employees of 3 permanent structures, Denmark (314)	Exposed reported significantly more symptoms than did nonexposed. Menstrual irregularities: Exposed, 35 Nonexposed, 0 Excessive thirst: Exposed, 60 Nonexposed, 5 Eye irritation: Exposed, 55 Nonexposed, 15 Headache: Exposed, 80 Nonexposed, 50	Formaldehyde levels in mobile day care centers: 0.24 to 0.55 ppm; permanent structures: 0.05 to 0.11 ppm
21 exposed workers in mobile home office, 18 nonexposed workers in another office, Illinois (315)	Exposed reported significantly more symptoms. Eye irritation: Exposed, 81 Nonexposed, 17 Throat irritation: Exposed, 57 Nonexposed, 22 Fatigue: Exposed, 81 Nonexposed, 22 Headache: Exposed, 76 Nonexposed, 11 No difference in pulmonary function	Formaldehyde levels in offices ranged from 0.12 to 1.6 ppm

Definition of abbreviations: A = adults; C = children.

* Complaint investigations were instigated at residents' requests.

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ticipated from the high water solubility of formaldehyde, acute mucous membrane and eye irritation are the most commonly reported symptoms in residents of mobile homes and homes insulated with UFFI (table 10). Many questions still remain, however, concerning other acute and chronic health effects of formaldehyde: human carcinogenicity, nonmalignant effects on the respiratory tract, and neurobehavioral impairment. Data on these issues derive largely from surveys of residents of mobile homes and homes insulated with UFFI (table 10), and from epidemiologic and clinical investigations of occupationally exposed workers.

Cancer. In 1979, the Chemical Industry Institute of Toxicology reported that rats exposed to formaldehyde developed nasal cancer, a tumor rarely found in control animals (316). This malignancy developed in 103 of 206 rats exposed to a concentration of 14 ppm and 2 of 235 rats exposed at 5.6 ppm. This first report of formaldehyde carcinogenicity in an animal model, which has subsequently been independently replicated (317), stimulated the rapid performance of epidemiologic investigations (table 11).

Because of its high water solubility, formaldehyde is primarily deposited in the upper respiratory tract, and cancer in this region is of primary concern. Halperin and coworkers (329) reported a case of nasal cancer in a worker exposed to formaldehyde for 25 yr in the textile-finishing industry. However, epidemiologic studies of mortality among formaldehyde-exposed professional and industrial groups have not provided consistent evidence of an association between formaldehyde exposure and upper respiratory tract cancer.

Retrospective cohort studies of formaldehyde-exposed workers have not shown an excess of nasal cancer (table 3) (323, 325-328). However, even the largest of these cohort studies (327) had only limited statistical power (80%), as calculated by the investigator, to detect a fourfold increase in risk for this rare cancer. Additionally, follow-up periods in these studies may have been too short if nasal cancer does not occur in excess until long after first exposure.

Several case-control studies of the association between formaldehyde exposure and nasal cancer have now been performed. In a hospital-based case-control study in the United States, Brinton and coworkers (330) demonstrated an association between nasal cancer and previous employment in the textile industry, an industry in which use of formaldehyde is widespread. They also found, however, that cases reported a history of formaldehyde exposure less frequently than did control subjects. A population-based case-control study of nasal cancer in Norway failed to show an association with occupations classified as involving potential exposure to formaldehyde (331), although the study was not originally designed to investigate formaldehyde's role. Because study subjects had not been asked directly about previous formaldehyde exposure, an industrial hygienist evaluated the occupational histories collected by interview and made a judgment on the likelihood of exposure for each subject. Vaughan and colleagues (332) employed a similar method of exposure assessment in a population-based study in western Washington. No association was detected between jobs with potential formaldehyde exposure and cancers of the pharynx, sinus, or nasal cavity.

In contrast, 2 other case-control studies have demonstrated a positive association between nasal cancer and potential formaldehyde exposure. In a recent Danish case-control study of nasal cancer, a list of patients with nasal can-

TABLE 11

STUDIES OF FORMALDEHYDE-EXPOSED COHORTS AND CANCER

Study	Findings	Comments
Cohort study of pathologists, Great Britain (318)	SMR elevated for lymphoma and hematopoietic neoplasms (211) but not for leukemia	Less than 10% of cohort deceased, less than 20 yr of follow-up
Proportional mortality study of embalmers, New York (319)	PMR significantly elevated for cancers of skin (221) and colon (143); nonsignificantly for cancers of brain (156) and kidney (150), and leukemia (140)	
Proportional mortality study of embalmers, California (320)	PMR significantly elevated for cancers of colon (188), brain (191), and prostate (176), and leukemia (174); nonsignificantly for bladder cancer (138)	
Cohort study of pathologists, Great Britain (321)	SMR significantly elevated for brain cancer (300) but not for lymphoma	Less than 5% of cohort deceased; 6 yr of follow-up
Cohort study of anatomists, USA (322)	SMR elevated for brain cancer (271, 95% CI = 130–499) and leukemia (148, 95% CI = 71–272)	Excess brain cancer persisted when psychiatrists used as a reference group
Cohort study of undertakers, Canada (323)	SMR nonsignificantly elevated for brain cancer (115) and leukemia (160)	20 yr of follow-up
Proportional mortality study of chemical plant employees, Massachusetts (324)	PMR nonsignificantly elevated for cancers of digestive organs (152) among formaldehyde-exposed workers. No data reported on brain cancer and leukemia	No evidence of trend of mortality in relation to exposure
Cohort study of chemical plant employees, USA (325)	SMR significantly elevated for cancers of genitourinary tract (169) SMR for leukemia not elevated No data for brain cancer	Case-control study within cohort showed no association between GU cancer and a general plant exposure
Cohort study of chemical plant employees, Great Britain (326)	SMR for lung cancer significantly elevated (124) in 1 of 6 men most highly exposed	Retrospective assessment made of level of exposure
Cohort study of industrial workers with formaldehyde exposure, USA (327)	SMR significantly elevated for nasopharyngeal cancer (318). SMR nonsignificantly elevated for lung cancer (111) and Hodgkin's disease (142)	Largest study reported to date, retrospective assessment of exposure level
Cohort study of garment workers, USA (328)	SMR significantly elevated for buccal cavity (343) and connective tissue cancer (364)	Retrospective assessment of exposure level

Definition of abbreviations SMR = standardized mortality ratio, PMR = proportional mortality ratio

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cer ascertained through a cancer registry was linked to employment data from a national pension fund that has covered all employees in Denmark since 1964 (333). Exposure was determined using a method similar to that employed in the Norwegian study. The investigators reported an association between nasal cancer and jobs with potential for formaldehyde exposure (relative risk = 2.8, for both males and females; 95% confidence interval = 1.8 to 4.3 for males and 0.5 to 14.3 for females). Adjustment for exposure to wood dust, which is associated with both nasal cancer and formaldehyde exposure, decreased the relative risk to 1.6 for males (95% confidence intervals = 0.7 to 3.6).

Hayes and coworkers (334) in the Netherlands studied 91 men with cancer of the nasal cavity and paranasal sinuses and 195 male control subjects. Potential formaldehyde exposure was assessed independently by 2 industrial hygienists who reviewed job histories obtained by interview. The relative risk for the association between formaldehyde exposure and nasal cancer was 1.9 or 2.5, depending on which industrial hygienist's assessment was used. The relative risk was highest for men with squamous cell carcinoma who had any exposure to formaldehyde but little or no exposure to wood dust (relative risk = 1.9 or 3.0).

Although the majority of studies performed to date have considered only occupational sources of formaldehyde exposure, a study of the relationship between residential formaldehyde exposure and nasal cancer has recently been reported. Vaughan and coworkers (335), in addition to obtaining job histories, also inquired about subjects' residential exposures to formaldehyde, including whether the subjects had ever lived in a mobile home. No association was found between residence in a mobile home and cancers of the oropharynx or hypopharynx or of the sinus and nasal cavity. However, an increased risk of nasopharyngeal cancer was associated with living in a mobile home. Residence in a mobile home for 1 to 9 yr was associated with a relative risk of 2.1 (95% confidence interval = 0.7, 6.6); the risk increased to 5.5 (95% confidence interval = 1.6, 19.4) when residence exceeded 9 yr. Although based on only 8 exposed cases of nasopharyngeal cancer, the association persisted after control for confounding by cigarette smoking and race.

Although an excess of nasal cancer has not been demonstrated in cohort studies of formaldehyde-exposed industrial workers, 2 recent studies provide evidence of a possible relationship between formaldehyde and buccal-pharyngeal cancer. Blair and coworkers (327) studied more than 26,000 workers employed in 10 different plants where formaldehyde was either used or produced. They reported a statistically significant excess of nasopharyngeal cancers (SMR = 318) and a nonsignificant excess of oropharyngeal cancer (SMR = 192), although there was no overall excess of buccal-pharyngeal cancers. Excesses of buccal cavity (SMR = 343), but not pharyngeal (SMR = 113) cancer, were noted by Stayner and colleagues (328) in a cohort study of garment workers exposed to formaldehyde. Unlike rats, humans breathe through their mouths as well as their noses. Thus, the buccal cavity may be a biologically plausible site for formaldehyde-induced cancer in humans.

The occurrence of lung cancer has also been examined in the formaldehyde-exposed cohorts, and an excess of lung cancer has been reported for 2 of the populations. Acheson and coworkers (326) studied 7,000 men employed in 6 different chemical and plastics factories. They found a 24% increase in lung cancer in one of the factories when national mortality rates were used as the standard of comparison but no significant increase when local rates were used. However, the lung cancer risk was greatest among men who started employment between 1935 and 1946, when exposures were highest. Additionally, the standardized mortality ratio was elevated only among men in the high exposure category. Blair and colleagues (327) reported a small and nonstatistically significant excess of lung cancer (the SMR was 111 for exposed workers, 93 for nonexposed workers). There was a statistically significant 32% increase among workers with more than 20 yr since first exposure. However, the investigators discounted the significance of this finding, noting that the excess did not increase with estimates of intensity or duration of exposure, or with cumulative exposure. Other studies have not found excess lung cancer in formaldehyde-exposed populations (319–324).

Cancers of other sites have also been examined in these investigations. Studies of embalmers (319, 320, 323), anatomists (322), and pathologists (318), but not of formaldehyde-exposed industrial workers (325–328, 336), have demonstrated significant excesses of brain cancer; excessive leukemia has also been found in embalmers (319, 320, 323), anatomists (322), and garment workers (328). Small excesses of Hodgkin's disease (327) and prostate (320), skin (319), kidney (319), connective tissue (328), and digestive system (319, 320, 324) cancers have been reported from individual studies, but they have not been confirmed by other investigations. Formaldehyde is rapidly metabolized and cleared from plasma; thus, the hypothesis that it causes cancer at sites distant from the point of absorption does not have strong biological plausibility (302).

At present, the epidemiologic data on the human carcinogenicity of formaldehyde are variable, and definitive conclusions cannot be reached. Formaldehyde exposure of subjects was not directly assessed in any of the studies; use of indirect measures may introduce random misclassification and reduce risk estimates towards unity, regardless of study design. Most of the cohort studies are limited by short duration of follow-up and by inadequate statistical power because of small sample sizes and small numbers of deaths. The case-control approach is appropriate for evaluating causes of a rare disease, such as nasal cancer. However, accurate retrospective documentation of exposure may be difficult. The proportional mortality method, used by Walrath and Fraumeni (319), Walrath (320), and Marsh (324), has inherent methodologic limitations (337); apparent excesses in one cause of death may be due to deficits in another. Further epidemiologic studies of the relationship between residential formaldehyde exposure and cancer should be undertaken.

Because the epidemiologic data are preliminary and inconsistent, risk assessment procedures have been used to describe the hazards of formaldehyde exposure. The Risk Estimation Panel of the Consensus Workshop on Formaldehyde (302) recommended that the epidemiologic data not be used for risk estimation and concluded that the animal data on nasal cancers were satisfactory for this purpose. Risk estimation requires the selection of a model to extrapolate from observed effects at high doses to the lower doses anticipated from human exposures at which effects cannot be directly identified. The choice of a particular risk assessment model may have a profound influence on the apparent risk of formaldehyde. The widely contrasting models and risk assessments recently published by the Chemical Industry Institute of Toxicology (338, 339) and by the Consumer Product Safety Commission (340) are illustrative.

The Risk Estimation Panel of the Consensus Workshop (302) proposed that

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formaldehyde should not be considered to have a threshold for cancer induction, but it did not strongly support any particular risk estimation model. Panel members agreed that the animal data from the Chemical Industry Institute of Toxicology Study were best described by a nonlinear model, but they were not able to specify the most appropriate nonlinear model. Different nonlinear models may produce differing estimates of risk at low doses, however. The panel considered that a simple linear model would provide a conservative upper bound for the risk at lower doses. Further research may provide new insight concerning the most suitable model and reduce the uncertainties concerning the human carcinogenicity of formaldehyde.

Nonmalignant Respiratory Effects. On the basis of studies of occupationally and domestically exposed populations, formaldehyde has been reported to cause excess respiratory symptoms, acute and chronic reductions of lung function level, and asthma. However, the evidence from these investigations is inconclusive.

Questionnaire surveys of symptoms have been performed on populations selected because of complaints about formaldehyde exposure at home or at work (table 10). These surveys show seemingly high prevalences of respiratory and nonrespiratory symptoms. The investigations of complaints in Washington, Wisconsin, Connecticut, and Texas cannot be readily interpreted because comparison populations were not evaluated and bias may have resulted from the selection of complaining subjects. The studies provide documentation, however, that formaldehyde exposure may occur in the domestic environment.

Thun and coworkers (313) used a more informative and less biased design in a study of 1,396 residents of homes insulated with UFFI and 1,395 residents of homes without UFFI. Subjects were selected from a roster of households insulated with UFFI rather than on the basis of symptom status. By telephone interview the investigators ascertained symptom prevalence over the previous year and the timing of symptom onset in relation to installation of UFFI. The prevalences of wheezing and burning skin were significantly higher in residents of homes with UFFI. Subjects who reported that odor had persisted for greater than 7 days after UFFI installation had the highest incidence of symptoms. The lack of formaldehyde measurements in the home, the low response rate, and the retrospective ascertainment of symptoms detract from the findings. However, this study represents one of the few population-based investigations of residential formaldehyde exposure in which study subjects were selected because of their potential for exposure rather than because of perceived health effects.

Norman and coworkers (341) examined the relationship of residence in a home insulated with UFFI to pulmonary function and respiratory symptoms in school children. Using data gathered during a previous study in Canada, the investigators identified children who had been living in homes with UFFI. Two children from homes without UFFI were matched to each exposed child (n = 29) on the basis of 9 variables that had been shown to predict pulmonary function. No association was found between exposure to UFFI and respiratory function or symptoms. Measurements of formaldehyde were not obtained.

Two studies have evaluated the effects of formaldehyde exposure in mobile homes used as offices (314, 315). Both studies included assessment of control populations and measurements of formaldehyde. Their findings were similar and demonstrated an excess of respiratory and nonrespiratory symptoms. Main and Hogan (315) also evaluated pulmonary function and found no effects of formaldehyde exposure; however, the study group included only 39 subjects.

Effects of formaldehyde on respiratory symptoms and pulmonary function have also been assessed cross-sectionally in occupational settings. Alexandersson and colleagues (342) studied 47 workers exposed and 20 workers not exposed to formaldehyde in a carpentry shop. Symptoms were ascertained by questionnaire, and spirometry was performed twice, once on Monday morning and again on Monday afternoon. The exposed workers reported "chest oppression" and symptoms of the eyes, nose, and throat significantly more often than the control subjects. The FEV_1, the FEV_1/FVC ratio, and the MMEF were normal on Monday morning but showed significant, although small, reductions over the working day in the exposed workers. These decrements, which occurred in both smokers and nonsmokers, were not related to the workers' personal formaldehyde exposures.

Levine and coworkers (343) surveyed symptoms and lung function in 90 morticians attending a continuing education course. Levels of spirometric parameters were not reduced in comparison to standard reference populations. When classified by extent of exposure, as estimated by the number of embalmings performed, the high and low exposure subjects did not differ on symptom prevalence or lung function level. Formaldehyde exposure was not measured directly, however.

Studies of workers exposed to phenol formaldehyde have also been considered to provide evidence on the effects of formaldehyde. Two studies with conflicting results have been published (344, 345). Industrial hygiene measurements documented the presence of other contaminants in these workplaces, and, thus, the results of these studies cannot be considered as relevant for domestic formaldehyde exposure.

Thus, current evidence for chronic effects of formaldehyde on lung function derives solely from several small cross-sectional studies. In a cross-sectional study, particularly for a highly irritating exposure such as formaldehyde, the most susceptible segment of the population is likely to be underrepresented. Further, the study populations were too small to detect any but large effects.

Formaldehyde has been reported to be a cause of occupational asthma (301, 346-348), although the mechanism of action is uncertain. Formaldehyde might cause asthma by specific immunologic sensitization or by induction of bronchoconstriction through nonspecific irritation (349); the relative importance of these 2 mechanisms has not been established. Medical (350, 351) and nonmedical publications have raised the concern that concentrations of formaldehyde found in residences may also be associated with asthma. Studies of persons exposed to formaldehyde in their homes have documented complaints of wheezing, chest tightness, and other symptoms compatible with asthma (table 10). However, cases of asthma resulting from domestic exposure to formaldehyde have not been published. In a unique documented case of a woman who developed asthma after installation of UFFI, the offending agent was found to be UFFI dust rather than formaldehyde (352).

Recent case series provide evidence on the role of formaldehyde as a cause of asthma at varying concentrations in the domestic and work environments. In these studies, subjects referred to a clinical facility for investigation of suspected formaldehyde-induced asthma were evaluated with bronchial provocation tests. Nordman and colleagues (353) reported that 12 of 230 workers referred to the Institute of Occupational Health

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in Finland had positive bronchial provocation tests when exposed to formaldehyde at 2 ppm. In England, Burge and coworkers (354) described 15 workers evaluated for occupational asthma. The investigators concluded that 3 subjects showed specific hypersensitivity to formaldehyde, 2 were affected through irritant mechanisms, and the remaining 10 subjects were probably affected by other agents.

Frigas and associates (355) evaluated 13 subjects referred for evaluation of possible asthma secondary to formaldehyde exposure in the work or home environment. As none of the 13 subjects responded to formaldehyde challenge, the investigators questioned the importance of formaldehyde as a cause of asthma at levels below 3 ppm, the range generally encountered in the domestic environment. However, because this series comprised only 13 subjects, firm conclusions on the role of formaldehyde cannot be drawn from its results. The findings of Nordman and colleagues (353) imply that at most one of the 13 subjects studied by Frigas and associates (355) would be expected to have formaldehyde-induced asthma.

These studies suggest that asthma may be mistakenly attributed to formaldehyde exposure and that the incidence of formaldehyde-induced asthma may be low. Although not widely available, specific bronchial provocation testing with formaldehyde is essential for diagnosis; the clinical history, while important for raising the initial concern about formaldehyde-related asthma, may be misleading.

Neuropsychologic and Behavioral Effects. Questionnaire surveys of symptoms in subjects concerned about formaldehyde exposure in their homes have documented a high prevalence of neuropsychologic symptoms, including headache, memory lapse, fatigue, and difficulty sleeping (table 10). The findings of more rigorous studies that included control populations have been similar.

Olsen and Dossing (314) compared the prevalence of symptoms among workers in mobile home day care centers with the prevalence among workers in 3 permanent structures. The workers in the mobile homes reported significantly more complaints of headache and unnatural fatigue, but memory and concentration did not differ in the 2 groups. Although acknowledging that the workers in the mobile homes were specifically concerned about their exposure to formaldehyde, the investigators concluded that biased reporting of symptoms was an unlikely explanation of their results. They based this conclusion on similar prevalences of symptoms unrelated to formaldehyde in the 2 groups.

In another cross-sectional study, Kilburn and coworkers (356) ascertained the frequency of neurobehavioral, mucous membrane, and respiratory symptoms among 76 histology technicians exposed to formaldehyde but also to xylene and toluene. In comparison with 56 secretaries and clerks, the histology technicians were more likely to experience disturbances of memory, sleep, balance, mood, concentration, and appetite. They were also more likely to report eye irritation, a reduced sense of smell, mucous membrane dryness and irritation, chest tightness, cough, shortness of breath, and palpitations. Each technician estimated the average number of hours per day of exposure to formaldehyde. The prevalence of most symptoms increased with lengthening exposure. Of 44 technicians who completed a 20-item depression scale, only 4 had scores suggesting depression. This study was initiated after discussions with histology technicians who were concerned about exposure to formaldehyde and solvents. Consequently, biased reporting of symptoms must be considered when interpreting the results of this study.

In order to measure neuropsychologic symptoms objectively, Schenker and associates (357) used standardized neuropsychologic tests in a study of 24 residents of 6 homes insulated with UFFI. Nine of 23 subjects reported neuropsychologic symptoms, including memory difficulty, headaches, difficulty concentrating, and emotional lability. Complaints of memory loss were not validated by formal tests. However, 11 of the 14 tested subjects demonstrated a deficit in their attention, and 9 of those 11 also had elevated depression scores. While use of objective tests of neuropsychologic function represents an improvement over questionnaire assessment of symptoms alone, the results of this study are, nonetheless, limited by the lack of a comparison population and the small number of study subjects.

The results of the complaint investigations indicate the need for a careful assessment of the neuropsychologic effects of formaldehyde exposure. The cross-sectional epidemiologic studies that have been undertaken involved small numbers of subjects, and their results are not definitive. Further laboratory investigation is needed to establish biological mechanisms that may underlie the neuropsychologic effects of formaldehyde. Formaldehyde might exert a direct toxic effect on the central nervous system. Alternatively, its odor could make those in contact with formaldehyde more aware of symptoms and more likely to attribute significance to them (302). The development and application of objective neuropsychologic tests to a population-based study group will be essential in clarifying the mechanism of formaldehyde's action.

Summary. Although the irritant properties of formaldehyde are documented, evidence on health effects at concentrations found in residences and offices is inconclusive. Respiratory effects and neurobehavioral impairment have been associated with formaldehyde exposure, but many of the studies may have been biased by the approaches used for subject selection and data collection. These health outcomes should receive further investigation in populations with measured exposure to formaldehyde that have been selected without bias. Appropriate control populations should be included in cross-sectional and cohort studies. Continued investigation of workers exposed to formaldehyde is needed to resolve the current controversy concerning carcinogenicity.

Clinically, formaldehyde should be considered as a potential cause of vague respiratory and neuropsychological symptoms and of asthma, but the diagnosis of formaldehyde-induced asthma should not be made without confirmation by inhalation challenge. Formaldehyde exposure may cause mucous membrane irritation in residents of mobile homes, new homes, and homes with potentially strong sources, such as new carpeting.

Volatile Organic Compounds

Volatile organic compounds (VOC) make up a large and diverse group of organic substances that share the property of volatilizing into the atmosphere at normal room temperatures. Formaldehyde, the VOC of greatest public and regulatory concern, has been extensively investigated in the past 10 yr (see previous section). However, hundreds of other VOC have been detected in indoor air (358, 359). Numerous sources of VOC exist in both residences and office buildings, including paints, adhesives, cleansers, cosmetics, building materials, furnishings,

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dry-cleaned clothes, cigarettes, gasoline, printed material, and other consumer products (359). Several studies describing sources and concentrations of VOC have now been completed (table 3).

Wallace and coworkers (359) recently summarized data from 9 studies collected in more than 1,000 homes in the United States and Europe. Although objectives and methodologies differed among the studies, all showed that concentrations of most organic compounds varied widely among homes and were substantially higher indoors than outdoors. The median indoor/outdoor ratio generally ranged between 2 and 5 for different compounds, but was as high as 10 for some compounds in some homes. In the most comprehensive investigation to date, investigators from the Environmental Protection Agency measured 12-h integrated exposures and breath levels of selected VOC in residents of 650 households in 6 communities throughout the United States (33, 359). This study included residents of Bayonne and Elizabeth, New Jersey, communities with petrochemical plants. Even in these communities, which have strong outdoor sources of VOC, levels of most halogenated and nonhalogenated compounds were 5 to 10 times higher indoors than outdoors.

While these studies document widespread exposure to VOC and emphasize the importance of indoor sources, they also demonstrate the difficulty in characterizing personal exposures to a complex mixture of compounds and in apportioning concentrations of specific compounds to specific sources. For example, in another Environmental Protection Agency study, VOC were monitored at 1 outdoor site and at 5 indoor locations in a home for the elderly. More than 350 different VOC were detected, 50 of which were common to all indoor locations. However, another 25 to 50 compounds were unique to each individual location (360). Lebret and colleagues (361) measured week-average concentrations of 45 VOC every other week in 4 homes for 26 wk. They reported that concentrations of some compounds were fairly stable over time, whereas others fluctuated widely. Gammage and coworkers (362) continuously monitored 40 homes in eastern Tennessee. They documented high peak concentrations of certain VOC after application of polishes, waxes, and cleaners. These peak concentrations decayed rapidly in most, but not in all, homes.

In all exposure assessment studies performed to date, concentrations of individual compounds have been an order of magnitude below the maximal permissible levels established for industrial environments. However, concern has been raised about the potential of VOC, even at low concentrations, to cause both acute and chronic effects. Some of the most commonly measured VOC are established or suspected mutagens and/or carcinogens. Additionally, many VOC are mucous membrane irritants, and VOC have been implicated as a cause of building-related illness (see section on building-related illness). Further, synergistic interactions among compounds may result in greater health impact than would be anticipated from simple additivity of effects.

Several experimental studies of the acute effects of VOC have been undertaken in the context of studying building-related illness (363, 364). Interpretation of these studies is limited by the nonspecificity of both the exposure and the symptoms, as well as by weaknesses in the study designs. Specific VOC responsible for health effects have not been isolated, and the nature of the relationship between VOC exposure and building-related illness remains unclear. However, further experimental investigations in which subjects are exposed to controlled concentrations of a single VOC and VOC in various combinations should increase our understanding of the relationship between VOC exposure and acute effects. Ultimately such studies, complemented by epidemiologic studies using comprehensive sampling strategies, can be expected to provide guidance on the need for regulations concerned with building design, building materials, and consumer products.

In contrast, epidemiologic studies of the chronic health effects of VOC are likely to prove extremely difficult. Adequate characterization of personal exposures is not currently feasible for a study of sufficient size and length to detect chronic health effects such as cancer. Consequently, assessment of the risk from chronic exposure to varying concentrations of VOC cannot depend on epidemiologic evidence. Further exposure assessment studies are needed to more fully describe concentrations and sources of VOC, to determine the most common VOC present, and to estimate the range and distribution of exposures in the general population. This information, in combination with toxicologic and experimental data, can provide estimates of risk for the formulation of environmental policies.

Building-related Illness

Introduction. Since the early 1970s, numerous outbreaks of work-related health problems have been described among employees in offices not directly contaminated by industrial processes. Two broad categories of episodes can be distinguished: those characterized by a generally uniform clinical picture for which a specific etiology can often be identified, and those in which affected workers report nonspecific symptoms temporally related to work. Symptoms reported in the latter outbreaks have typically included mucous membrane and eye irritation, cough, chest tightness, fatigue, headache, and malaise. In outbreaks with an identified etiology, a wide spectrum of causative factors has been implicated: immunologic sensitizing agents, infectious agents, specific air contaminants, and environmental conditions, such as temperature and humidity (248, 365). Outbreaks without an identifiable etiology have frequently occurred in new hermetically sealed office buildings and have been called "tight building syndrome" (TBS) or "sick building syndrome."

Terminology for these episodes is not uniform. For the purpose of clarity, we will use the phrase "building-related illness" as an inclusive term to refer to all epidemics of illness occurring in nonindustrial workplaces. We will restrict our use of the term "tight building syndrome" to those epidemics of building-related illness that do not have a specific etiology. We recognize, however, that this term may be somewhat misleading, as some of these epidemics occur in buildings that are not tightly sealed.

Exposures in the Office Environment. New construction techniques and ventilation practices directed at conserving energy have led to increasing problems with air quality in the office environment; the resulting buildup of pollutants is undoubtedly a factor in building-related illness. Many multistory office buildings built since 1965 are constructed with an internal structural support surrounded by a thin continuous outer envelope. The external shell is hung from the central core and usually consists of prefabricated components with sealed windows. This technique is often less expensive than alternatives, and the external shell provides a barrier to uncontrolled infiltration of outside air. Air movement into the modern office building is controlled entirely

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through a heating, ventilation, and air-conditioning system that usually cannot be controlled directly for any particular space by its occupants. Frequently, to maximize the extent of usable floor space, the heating, ventilation, and air-conditioning system is located on the rooftop. Such systems tend to be designed to operate over a smaller range of ventilation than systems installed within a structure.

The reduced ventilation rates in modern office buildings may lead not only to a generalized air quality problem but to the development of specific localized problems. The majority of buildings are operated at a positive pressure with regard to outside air. Morris and Wiggin (366) have warned that lowering the static pressure in buildings may actually deprive upper floors of fresh air through a buoyancy or "chimney effect." In some buildings, reduction of operating pressure may result in entry of air from polluted locations, such as underground parking garages, and from exhaust vents placed near the street.

For decades, buildings were constructed with constant air flow volume systems that were designed to heat or cool the space within the building. In newer and more tightly sealed buildings, internal sources, such as lights, machines, and people, may suffice to heat the air. In these buildings, air delivery rates are varied to maintain the temperature and not necessarily to meet air quality needs.

The rapid increase in energy prices in the 1970s led to a reevaluation of ventilation standards and operating practices. As a result, fresh air supplies were frequently reduced to a minimum in office buildings. The American Society for Heating, Refrigerating, and Air Conditioning Engineers revised its recommended ventilation standard for fresh air supply in the absence of smoking (367), recommending 10 cubic feet per minute (cfm) per person. The guidelines recommend between 20 and 30 cfm per person for spaces where smoking is permitted. The economic incentives for reducing the fresh air supply are evident. Depending on local utility prices and climate, the annual cost of supplying and conditioning a cubic foot of air per minute may range from $2.00 to more than $4.00 in most locales. Schools, office buildings, and arenas often require fresh air supply rates greater than 100,000 cfm.

The office environment contains numerous sources of potentially hazardous air pollutants. Cigarette smoking, unvented combustion emissions, and vehicle exhaust may add particles and gases to the air in an office. VOC may be released from adhesive, tiles, vinyl wall coverings, rugs, office furniture, and wet-process copying machines. Solvents, cleansers, pesticides, and fibers may also contaminate the air in an office.

Bacteria and fungi may grow on wet surfaces, air conditioners, ducts, filters, and humidifiers. In the past, disease outbreaks in office workers caused by bacteria and fungi were most common in the winter and possibly were related to recirculation of air. More recent outbreaks of disease have often occurred during the time that coolers are in use; the ventilation system may disseminate microorganisms that proliferate in the drip pans under condensing coils or in the water reservoir of a cooling system. The standing water provides a suitable environment for a variety of microorganisms; the specific organisms that proliferate depend upon available nutrients, the pH of the water, and the temperature of the water. After growth of organisms begins, metabolic products may provide nutrients for other organisms and support a growth chain that includes bacteria, fungi, algae, and amoebae. A slime of viable and dead organisms and spores may develop (368). This material may become aerosolized and distributed by the ventilation system.

Building-related Illness. Outbreaks of illness in office buildings related to some of the specific etiologic agents mentioned above have occurred for many years. However, a new problem, characterized by reports of nonspecific symptoms among building occupants that could not be attributed to specific agents, was first reported in the late 1970s. This problem was soon designated "tight-building syndrome."

TABLE 12

CLASSIFICATION* OF THE ETIOLOGY OF BUILDING-RELATED ILLNESSES IN 356 HEALTH HAZARD EVALUATIONS CONDUCTED BY THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH THROUGH DECEMBER 1985

Etiology	(n)	(%)
Inside contaminants	67	19
Outside contaminants	38	11
Contaminants from building materials	14	4
Biological contaminants	19	5
Inadequate ventilation	179	50
Unknown	39	11

* See text for definitions. Data provided by Kenneth Wallingford, personal communications.

To date, most of the information on building-related illness derives from health hazard evaluations conducted by federal and state agencies rather than from formal epidemiologic studies. As of December 1985, the National Institute of Occupational Safety and Health (NIOSH) had completed 365 health hazard evaluations of building-related problems (Kenneth Wallingford, personal communications). These evaluations were not conducted according to a standardized protocol until recently, and their classification by etiology was based on a review of written reports (309). Nevertheless, the results of the health hazard evaluations illustrate the heterogeneous etiologies of problems related to office buildings.

Indoor contaminants were cited as the primary cause of building-related illness in 19% of episodes (table 12). This diverse category included all chemical contaminants, such as copying machines, carbonless copy paper, and tobacco smoke, generated by indoor sources. Contaminants from outdoor sources, such as motor vehicle exhaust or dust from construction, may be drawn into a building through intake vents. In 4% of cases, contaminants from building materials and products, such as formaldehyde from new furnishings and fibrous glass from lined ventilation ducts, were considered to be the responsible agents. The biological contaminants were primarily associated with hypersensitivity pneumonitis.

However, in 179 of the 356 investigations, no specific causal agent other than inadequate ventilation could be identified. Because ventilation measurements were performed rarely in the earlier investigations, this categorization was often based on questionnaire data or on exclusion of other causes. In the more recent investigations, ventilation has been evaluated directly by measuring air flow or indirectly by examining building specifications. Standards developed by the American Society for Heating, Refrigerating, and Air Conditioning Engineers for ventilation and thermal environment have been used as a basis for comparison. However, the specific mechanisms through which inadequate ventilation produces tight building syndrome are unclear.

Recent epidemiological investigations have further characterized the dimensions of tight building syndrome. Finnegan and coworkers (369) determined symptom prevalence in workers in 9 of-

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TABLE 13

PREVALENCE (%) OF SYMPTOMS IN BRITISH WORKERS IN RELATIONSHIP TO THE AIR SUPPLY IN THEIR OFFICE BUILDINGS*

	Type of Air Supply			
Symptom	Natural Ventilation ($n = 259$)	No Humidification Air Recirculation ($n = 73$)	Humidification No Air Recirculation ($n = 354$)	Humidification Air Recirculation ($n = 477$)
Nasal	5.8	13.7†	22.4‡	17.2‡
Eye	5.8	8.2	28.3‡	17.6‡
Mucous membrane	8.1	17.8†	37.9‡	32.6‡
Tight chest	2.3	1.1	9.6‡	7.8‡
Shortness of breath	1.6	—	4.3	2.9
Wheeze	3.1	—	5.1	4.4
Headache	15.7	37.0‡	34.7‡	39.5‡
Nosebleed	0.5	—	1.4	2.2
Dry skin	5.7	5.5	16.2‡	14.9‡
Rash	1.9	2.7	3.1	2.9
Itchy skin	2.9	2.7	7.4†	7.2†
Lethargy	13.8	45.2‡	49.9‡	52.5‡

* Based on table II in reference 366. Series included 3 buildings with mechanical ventilation, one with no humidification and air recirculation, 2 with humidification and no air recirculation, and 3 with humidification and air recirculation.
† $p < 0.05$ in comparison with workers in the natural ventilation building.
‡ $p < 0.01$ in comparison with workers in the natural ventilation building.

fice buildings, 3 with natural ventilation, and 6 with mechanical ventilation (table 13). The symptoms were ascertained by questionnaire and considered work-related if onset or worsening was related to working in the building. Symptoms compatible with tight building syndrome were significantly more common in workers in each of the mechanically ventilated buildings. Selection bias cannot explain these findings, as 7 of the 9 buildings were chosen by the investigators for study without prior knowledge of building-related problems. The results of this study also illustrate the potential for selection bias in studies of tight building syndrome; symptom rates in workers in the 2 buildings selected because of complaints were higher than rates in the buildings selected by the investigators.

In a subsequent study, this same investigative group surveyed workers in 2 buildings, one naturally ventilated, and the other mechanically ventilated (370). The prevalences of rhinitis, nasal blockage and dry throat, lethargy, and headache were significantly higher in workers from the building with mechanical ventilation. Measurements of temperature, humidity, air velocity, ion concentrations, CO, O_3, and formaldehyde did not differ between the 2 buildings.

The findings from the health hazard evaluations and the cross-sectional epidemiologic studies implicate ventilation as contributing to tight building syndrome. It remains unclear whether the effects of reduced ventilation are mediated directly by alterations in comfort or indirectly by causing the buildup of other pollutants. Monitoring of offices with work forces affected by tight building syndrome has not shown that concentrations of specific pollutants exceed accepted standards (370, 371).

VOC have been considered as one possible cause of tight building syndrome (372) (see section on VOC). With new analytical methods, hundreds of VOC have been found in indoor air (358, 359), usually at concentrations substantially lower than those permitted in the workplace. However, VOC are generally present in complex mixtures, which might produce health effects even though none would be anticipated on the basis of individual VOC concentrations. Further, the irritant properties of VOC make them plausible etiologic agents for many of the symptoms of tight building syndrome. Many of the known VOC could contribute to the eye, mucous membrane, and respiratory tract irritations common in tight building syndrome.

Data from recent experimental investigations lend support to this hypothesized role of VOC. Ahlstrom and colleagues (373) exposed healthy volunteers to 0.82 ppm of formaldehyde in a chamber. Varying percentages of air from a building where workers had been affected by tight building syndrome were added to the chamber. Symptoms of mucous membrane irritation were 4 times more common when the percentage of air from the office building was increased from 10 to 100%.

Molhave and coworkers (363) exposed 62 healthy volunteers, all of whom had previously complained of symptoms typical of tight building syndrome, to a mixture of 22 VOC commonly found in indoor air. Exposure concentrations were zero, 5, and 25 mg/m³, corresponding to concentrations found in clean air, in air normally present in new houses, and in very contaminated indoor air, respectively. In a double-blind design, each subject was exposed to a concentration of zero mg/m³ and to a concentration of either 5 or 25 mg/m³ of mixed VOC. Subjects' perceptions of air quality, odor, and symptoms were assessed by questionnaire. Subjects rated the air quality unacceptable and reported symptoms of nose and throat irritation and inability to concentrate significantly more often when exposed to either 5 or 25 mg/m³. Additionally, the investigators objectively evaluated the participants' responses to different exposure levels using the digit span test, the graphic continuous performance test, and a trigeminal nerve irritation test (364). Performance on the digit span test, which measures ability to concentrate and short-term memory, was impaired at both exposure levels; other tests were normal.

Interpretation of these reports is limited by their preliminary nature. Little data were provided, and estimates of effect were not presented. Moreover, the study subjects were selected from a pool of 287 subjects who had all experienced "indoor climate symptoms," primarily irritation of the eyes and upper airways. Thus, these subjects may represent a population particularly sensitive to indoor pollutants. Finally, the odor of the exposure would necessarily limit the degree to which the study could be conducted in a double-blind fashion.

The findings of a recent experimental study suggest that both inadequate ventilation and VOC play a role in tight building syndrome. Sterling and Sterling (372) hypothesized that the nonspecific symptom complex characteristic of tight building syndrome is caused by indoor photochemical smog generated by the action of ultraviolet radiation from fluorescent lights on VOC in indoor air. To test this hypothesis the investigators studied the occupants of 2 buildings, one mechanically ventilated and the other naturally ventilated. On the initial symptom survey, the investigators documented a higher prevalence of nonspecific symptoms in workers in the mechanically ventilated building. Subsequently, the employees completed a questionnaire on

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symptoms and environmental quality twice a week during the 10-wk study period.

Without the employees' knowledge, the investigators varied the percentage of fresh air entering the mechanically ventilated building and replaced the lights with standard cool white fluorescent lights. During the period that a greater percentage of fresh air was circulated, the employees reported an improvement in environmental quality, including better air movement, decreased stuffiness, and more comfortable temperatures. Symptoms of eye irritation decreased 6.8% when the ventilation was changed, 8.0% when the lighting was changed, and 31.2% when both were changed simultaneously. Negative perceptions of environmental quality and reports of eye irritation rose to the levels documented at the start of the experiment when the ventilation and lighting were restored to their original state.

Neither epidemiologic nor experimental studies have identified specific etiologic agents for tight building syndrome. While the experimental studies suggest that low concentrations of VOC in sealed buildings lead to the symptoms of irritation found in tight building syndrome, concentrations of VOC have not been measured in buildings with affected and unaffected work forces. Several investigators have also suggested that high stress levels, precipitated by inability to control environmental conditions in a sealed building, poor labor-management relationships, or other human factors may contribute to building-related illness (308, 374). While such psychological factors may contribute to tight building syndrome, their roles have not been addressed in formal studies. Assessment of the role of psychological factors in tight building syndrome will be difficult; these factors are difficult to quantify and likely to change after tight building syndrome occurs.

Summary. Continued health hazard evaluations of episodes of building-related illnesses are needed to establish the dimensions of the problem and to identify specific and remediable causes. Evaluations of new outbreaks would be more informative if standardized methods were developed and adopted for assessment of exposures and health outcomes. However, studies limited to buildings with affected work forces cannot fully elucidate the causes of tight building syndrome. Additional epidemiologic and experimental studies are needed. Experimental studies in which volunteers are exposed to measured amounts of suspect agents, singly and in combinations characteristic of those found in problem buildings, will help narrow the list of possible etiologic agents. Epidemiologic investigations must not only address health outcomes, but they also must include a comprehensive assessment of engineering, air quality, and psychological aspects of the workplace. Both cross-sectional and longitudinal investigations may be informative if combined with a comprehensive environmental characterization.

Clinically, the diagnosis of a building-related illness should be considered in persons with appropriate symptoms and employment in a sealed building. However, criteria for making this diagnosis in an individual patient have not been established.

Radon and Radon Daughters

Introduction. Exposure to radon daughters, the short-lived decay products of radon, places uranium and other underground miners at an increased risk for lung cancer (15, 375–377). While the lung cancer risk incurred by underground miners has been recognized for a century, the hazard posed by environmental radon and radon daughters has only recently been investigated. Because radon daughters are invariably present in indoor air, exposure to them may be a risk factor for lung cancer in smokers and nonsmokers in the general population. In fact, the lung dose from inhaled radon daughters is the highest to any organ from natural background radioactivity (376).

Uranium and radium, a member of the uranium decay series, are present in all rocks and soils, although the concentrations vary widely (376, 378). Radium decays to radon, a noble gas. Because radon is inert, it can diffuse out of the material in which it forms and enter the atmosphere or dissolve in surrounding water. Radon decays with a half-life of 3.82 days into a series of short-lived solid isotopes collectively referred to as radon daughters (378, 379). The series of daughters includes Po-218, Pb-214, Bi-214, and Po-214, with half-lives ranging from less than 1 s to 26.8 min, and terminates with Pb-210, a more stable radionuclide with a half-life of 22 yr. Two of the daughters, Po-214 and Po-218, emit alpha particles during decay.

Alpha-decay of inhaled radon daughters while in the respiratory tract is thought to induce the tissue injury that eventually results in malignancy. Although the daughter products release alpha, beta, and gamma energy during their decay, the dose of radioactivity to the lung is due almost exclusively to the alpha particles released by polonium-218 and polonium-214 (377, 380). The alpha particles are presumed to penetrate the epithelial lining of the lung directly and damage the genetic material of the basal cells.

For historical reasons, the concentration of radon daughters is generally expressed as working levels (WL), where 1 WL is any combination of radon daughters in 1 L of air that ultimately releases 1.3×10^5 MeV of alpha energy during decay (379). A concentration of 1 pCi/L of radon translates to about 0.005 WL in a home. Exposure at 1 WL for 170 h equals 1 working level month (WLM) of exposure. The WLM was developed to describe exposure sustained during the average number of hours spent underground by miners. Because most persons spend much more than 170 h in their homes each month, a concentration of 1 WL in a residence results in an exposure much greater than 1 WLM on a monthly basis.

Exposure to Radon. The predominant source of radon in indoor air is the soil beneath structures (376, 381). Radon diffuses through the ground into basements and crawl spaces, and then throughout the air in a home. Other sources include utility natural gas and water used within the home. In homes supplied with water from deep wells in granite rock, radon concentrations may be increased by release of radon that has been dissolved in the water. Short-term variation in the concentration of radon within a home results from changes in air exchange rates, varying meteorologic conditions, and use of water and natural gas.

Radon concentrations have not yet been measured within a large random sample of U.S. homes, although surveys have been undertaken in other countries. Typical radon concentrations range from 0.01 to 4 pCi/L, and much higher levels have been measured in some homes (figure 3). Use of building materials that contain high concentrations of radium and construction of homes on geologic formations composed of granite rich in radium may lead to particularly high levels of radon. Extremely high concentrations of radon have been found in some homes built over the Reading Prong, a geologic formation in eastern Pennsylvania, New Jersey, and Maryland. Some

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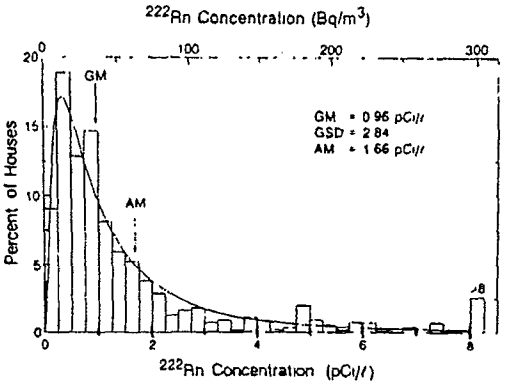

Fig. 3. Frequency distribution of radon concentrations compiled from selected samples of U.S. homes. Reprinted with permission from reference 379.

conventional homes in Maryland and Pennsylvania have integrated radon concentrations exceeding 20 pCi/L.

Nero (382, 383) examined 35 data sets of radon measurements taken in the United States and identified 22 that provided unbiased data on radon in single family homes. The distribution was similar to that in figure 3, with an average concentration of approximately 1.5 pCi/L; 1 to 3% of the homes exceeded 8 pCi/L. On the basis of this analysis, Nero has suggested that more than 1 million U.S. homes may have annual average radon concentrations exceeding 8 pCi/L.

Lung Cancer and Radon Exposure. Numerous studies of uranium miners and other underground miners have now established a causal association between exposure to radon daughters and lung cancer (375, 384). Animal studies confirm that exposure to radon daughters alone causes lung cancer (377). The human data have come primarily from miners with high exposures to radon daughters, and the risks of lower exposure levels have not yet been well characterized. The shape of the exposure-response relationship between radon daughter exposure and lung cancer risk also has not been established. Other unresolved issues are the lung cancer cell types associated with radon daughter exposure and the nature of the interaction between cigarette smoking and radon daughters.

The relationship between exposure, measured as WLM, and dose to the target tissues in the lung, measured as rads or grays, is extremely complex. Determinants of tissue dose include physical factors, such as the characteristics of the carrier aerosol, the proportions of attached and unattached radon daughters, and the degree of radon daughter equilibrium, as well as biological factors, such as the pattern of respiration, the pattern of particle deposition and clearance, and the locations of the target cells for cancer induction (377, 380). Further, a quality factor for alpha radiation is necessary to convert rads to rems, or grays to sieverts.

These dosimetric considerations suggest that WLM sustained in a mine and in a residence may not yield equivalent tissue doses. Generally, mines are dustier than homes, equilibrium fractions of radon daughters may differ in the 2 environments, the minute ventilation is higher during mining and other underground labor than during normal activities in a home, and the prevalence of respiratory tract abnormalities related to cigarette smoking and other environmental agents may differ in miners and nonminers. Further, exposure to radon daughters in the domestic environment begins at birth, and the anatomy of the child's lung tends to increase dose to the bronchi (377). The effects of these determinants of tissue dose have been examined by computer-modeling techniques. These analyses do not indicate large differences between tissue dose in environmental and occupational settings and support the use of the WLM to describe environmental exposure (377, 385, 386).

To date, epidemiologic investigations of domestic radon daughters as a risk factor for lung cancer have been limited and preliminary. Both descriptive and analytical approaches have been used to examine the association between radon daughter exposure in the home and lung cancer. Techniques for estimating lifetime exposure of persons to radon daughters from indoor air are not yet available, and surrogates based on residence type or on limited measurements have been used in the analytical studies.

In the descriptive studies, incidence or mortality rates for lung cancer within geographic units have been correlated with measures of exposure for inhabitants of these units. Edling and associates (387) compared mortality rates for different Swedish counties with background levels of gamma radiation, which they described as correlated with indoor exposure to radon and its daughters. The correlation coefficients were 0.46 for males and 0.55 for females. Hess and colleagues (388) performed a similar analysis for lung cancer mortality from 1950 to 1969 in the 16 counties of Maine. Using average radon concentrations in water as the measure of exposure, they calculated correlation coefficients of 0.46 for males and 0.65 for females. In a study of 28 Iowa towns served by deep wells, lung cancer incidence increased with the level of radium-226, the source of radon, in the water (389). These descriptive studies, which do not consider the exposures of persons to radon daughters and other agents, can provide only suggestive evidence that radon daughter exposure in the home increases lung cancer risk.

This association has been more directly tested in case-control and cohort studies. Axelson and associates (390) conducted a case-control study with 37 lung cancer cases and 178 control subjects from a rural area of Sweden. Radon daughter exposure was inferred from the characteristics of the subjects' residence at the time of death. Those who lived in stone houses were assumed to be most exposed and those who lived in wooden houses were assumed to be the least exposed, and other types of dwellings were considered to be a source of intermediate exposure. Despite this crude exposure classification, residency in stone houses was associated with a significantly increased odds ratio (age- and sex-adjusted odds ratio = 5.4) in comparison with the reference category of wooden houses. Data concerning cigarette smoking and lifetime residence history were not considered.

In another case-control study in rural Sweden, the study subjects were residents of the island of Oeland, deceased during the period 1960 to 1978 (391). The geologic characteristics of the island were thought to result in strong variation of background radon concentrations within a small area. Inclusion in the study population required at least 30 yr of residence at the same address before death; 23 lung cancer cases and 202 control subjects dead from causes other than lung cancer

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met this criterion. Most of the dwellings were monitored for radon daughters during 3 months of summer and 1 month of winter. The dwellings were also classified on the basis of structural characteristics as in the earlier study of Axelson and associates (390), and cigarette smoking information was obtained from next of kin. Lung cancer risk was significantly associated with radon daughter exposure, as assessed by either the measured concentration or the characteristics of the dwelling, and both crude and smoking-adjusted risk estimates were significantly increased.

Pershagen and coworkers (392) reported the findings of 2 small case-control studies in Sweden on domestic radon daughter exposure; one was drawn from a larger study in northern Sweden, and the other from a twin registry. The investigators assembled each series with 30 case-control pairs divided equally between smokers and nonsmokers. Exposure to radon was estimated from information on dwelling type; the investigators attempted to consider all residences. In the study group from northern Sweden, radon exposures were significantly higher in the smoking cases than in their smoking controls. Estimated exposures were similar in the nonsmoking cases and control subjects in the series from northern Sweden and in the smoking and nonsmoking cases and control subjects in the second series selected from a twin registry.

In the United States, Simpson and Comstock (393) examined the relationship between lung cancer incidence and housing characteristics. During a 12-yr period in Washington County, Maryland, lung cancer incidence in the county's residents was not significantly affected by type of basement construction or building materials. Without specific validation, these dwelling-related variables were assumed to be surrogates for radon daughter exposure.

Because only scant and limited epidemiologic data are available, the hazard posed by radon daughter exposure in indoor air has been addressed primarily through risk estimation procedures. To assess the consequences of exposure by using risk estimation techniques, information on the population distribution of radon daughter exposures in dwellings must be combined in a risk projection model with coefficients that describe the increment in lung cancer occurrence per unit exposure in a risk projection model. For the United States and most other countries, however, the necessary data on radon daughter concentrations are not yet available. The selection of risk coefficients for radon daughter exposure is also problematic. The mining populations that have been studied generally received much higher exposures than arise from the usual environmental sources, and each study has methodologic limitations, particularly with regard to the quality and extent of information on exposure (377, 384, 394, 395). Risk coefficients have also been developed with dosimetric approaches (377, 396).

To perform the risk estimation, a mathematical model must be selected to project the lung cancer cases associated with the exposure to radon daughters. Risk projection models require assumptions concerning the temporal expression of the associated lung cancer cases attributable to radon daughters as well as to the effects of potentially important cofactors, such as age at exposure, age at risk, and cigarette smoking. The 2 most widely applied models are the relative and attributable risk models; the former assumes that the background risk is multiplied by the effects of radon daughter exposure, whereas the latter assumes the addition of the excess risk to background. Thomas and McNeill (394, 395) suggest that the relative risk model is most appropriate for radon daughter exposure and lung cancer.

Estimates of the effect of exposure to environmental radon daughters have been made on the basis of risk models that have varying underlying assumptions (table 14). While the input information for these models may have identified limitations, risk assessment represents the only currently feasible approach for evaluating the extent of the hazard associated with environmental radon and radon daughters. The results of the models indicate that environmental radon daughter exposure poses a substantial risk to the general population. Of approximately 135,000 lung cancer cases annually in the United States, about 10,000 may be attributable to radon daughter exposure; alternatively, about 20% of the lifetime risk of lung cancer in nonsmokers, estimated as 1%, may be explained by radon daughters. These projections, however, are based on average exposures of populations, and individuals may incur much higher risks if they reside in homes with particularly high radon concentrations. New results from studies of miners, in combination with population surveys of radon exposure, should provide more refined risk estimates in the future.

The manner in which radon daughter exposure and cigarette smoking are assumed to interact strongly influences the results of such risk estimation models. If a multiplicative interaction is assumed, then the risks for smokers, already much greater than for nonsmokers, are multiplied by the additional risk from radon daughter exposure. If the interaction between smoking and radon daughter is additive, then the excess risk for smokers is given by the sum of the additional risks incurred by smoking and by radon daughter exposure. The interaction between the

TABLE 14

SELECTED RECENT PROJECTIONS OF THE LUNG CANCER RISK ASSOCIATED WITH ENVIRONMENTAL RADON DAUGHTER EXPOSURE

Author	Risk Projection Model	Findings
Cohen (397)	Attributable risk projection model using various risk coefficients and assuming a mean exposure of 0.22 WLM/yr	Author's best estimate is 10,000 cases/yr
Evans et al. (398)	Attributable risk projection model with lifetime risk coefficient of 10^{-4}/WLM chosen as "most defensible upper bound"	Mean lifetime exposure of 12 WLM gives risk of 0.12%
Steinhausler et al. (399)	Attributable risk projection model with coefficients from 1977 UNSCEAR report; exposures estimated from sampling in Salzburg, Austria	Based on exposure profile, authors' estimate that 15% of lung cancer in Salzburg may be from radon daughters
NCRP Report No. 78 (377)	Combination of dosimetric approach and attributable risk projection model	Lifetime risk for exposure of 0.2 WLM/yr estimated as 0.18%; authors' estimate 9,000 attributable lung cancer deaths annually in U.S.
Thomas et al. (395)	Relative and attributable risk models under varying assumptions; risk coefficients based on literature review and reanalysis of published data	Additional domestic exposure at 0.02 WL from birth causes 2 excess lung cancers per 100

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2 agents might take some form other than the purely additive or multiplicative. The presently available epidemiologic evidence indicates an interaction between cigarette smoking and radon daughter exposure that is greater than additive, though the data are not uniformly conclusive (377, 394).

The hypothesis has been advanced that radon daughters directly contribute to the development of lung cancer in both active smokers and in nonsmokers passively exposed to tobacco smoke (400–402). The arguments are complex and will be considered here only for the case of passive smoking. Unquestionably, tobacco smoking increases the concentration of respirable particulates in enclosed spaces. Bergman and coworkers (403, 404) have shown that the introduction of cigarette smoke leads to greater build-up of radon daughters in an unventilated room. Bergman and coworkers interpret this finding as reflecting attachment of daughters to tobacco smoke aerosol, which retards removal by adhesion to room surfaces. Increased exposure to radon daughters would, thus, result from the cigarette smoke. Martell and Sweder (400) and Martell (405) have argued that tobacco smoke increases the concentration of larger particles, which are more likely to be deposited at bronchial bifurcations than the smaller particles present inside uncontaminated, well-ventilated structures.

These speculations require further investigation, and the premises of Martell have been questioned (406). Further, the results of dosimetric modeling indicate that increasing concentrations of particles may decrease the dose received by the basal cells in the tracheobronchial epithelium (377). The dose to these cells falls as the unattached fraction of radon daughters declines. Accordingly, the net effect of tobacco smoke aerosol on the risk of inhaled radon daughters represents the summation of factors tending to increase and decrease dose to target cells. Available data are not sufficient to support a conclusion on the balance of these factors.

TABLE 15

CONTROL MEASURES FOR POLLUTANTS

Pollutant	Control Measures: Equipment and Materials	Control Measures: Ventilation and Design
Respirable particles	High efficiency filters Tight sealing doors and grates Properly drafting chimney Electrostatic precipitators	Zone and ventilate for smoking Supply outside combustion air to heater and fireplace Relocate air intakes Maintain filter system
NO, NO_2	Remove gasoline engine Pilotless ignition	Effective hood vent over source Isolate garage from indoor space
CO	Pilotless ignition Restrict heater use to uninhabited space Use catalytic converter Replace indoor gasoline engines with electric	Supply outside combustion air Vent emission outside Kitchen/hood vent Relocate vents Provide smoking zones Isolate garage from indoor space
CO_2	Check static pressure in return air ducts to make sure return is not overriding fresh air intake	Isolate garage from indoor space
Agents from biological sources	Insulate to prevent condensation Damp-proof foundation, ducts Proper drainage of drip pans under condenser coils Add bacteriocides to steam and water for humidifiers and cooling towers Proper maintenance of filters and ducts Routine cleaning Discard water-damaged floor coverings Do not use cool-mist humidifiers and vaporizers	Maintain inside relative humidities of 35–50% Exhaust bath and kitchen Vent crawl spaces
Formaldehyde	Substitute products such as phenolic resin plywood Seal sources Removal of materials	Increase air exchange to house or office
Radon and radon daughters	Vapor barrier around foundation Damp-proof basement and crawl space Seal cracks and holes in floor traps and drains Install charcoal water-scrubber for well water Completely seal foundation	Vent crawl space Vent sumphole to exterior Subslab depressurization Subslab depressurization Vent bathroom and laundry to exterior
Volatile organic compounds	Substitute products Isolate storage area Apply only according to specifications Do not locate transformers indoors	Use only with adequate ventilation Ventilate laundry, shop Provide separate ventilation to storage area
Asbestos	Removal Injection sealant Wrap pipes with plastic and duct tape	Ventilation does not provide adequate protection

Control of Indoor Air Pollution

Introduction

In this section, we briefly consider the diverse options for achieving acceptable concentrations of air contaminants indoors (table 15). A more comprehensive treatment can be found in the National Research Council's report on indoor air quality (15). Sources may be removed, relocated, or mitigated. Ventilation may be increased to reduce pollutant concentrations throughout a structure or in specific areas. Pollutant concentrations may also be reduced by air cleaning devices, which operate by filtration, adsorption, absorption, electrostatic precipitation, or by other principles. Such devices may be applied to exhaust from the pollutant source, to recirculated air, to the supply air, or to air within the occupied volume.

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Source Alteration

While removal of pollutant sources represents the most definitive control method, it is not practicable in many instances. For many sources, evidence of health effects of the released pollutant is not sufficiently compelling; for others, removal may not be feasible. Personal choice may reduce contact with some sources, such as tobacco smoking and woodburning.

Ventilation

In many circumstances, increased air exchange in either a specific zone or throughout a structure effectively reduces pollutant concentrations. Local exhaust of photocopying rooms, areas where smoking is permitted, kitchens, basements, sump-pump areas, and bathrooms reduces pollutant concentrations at relatively low cost. However, zone ventilation is ineffective for emissions that originate from many locations or from materials used throughout a structure. For such widespread sources a localized source of fresh air or alteration of building-use patterns may create zones of adequate air quality. More often, ventilation must be increased throughout the structure.

The extent to which ventilation should be increased is uncertain, although American Society of Heating, Refrigerating, and Air Conditioning Engineers standards provide some guidance. Although 5 cfm per person is twice the ventilation needed to maintain CO_2 concentrations below 0.5%, this organization recommends 7 to 10 cfm for most indoor environments where smoking is not permitted (367). Because of widely varying sensitivity to microorganisms, organic irritants and odorants, and other indoor pollutants, 7 to 10 cfm per person may not provide a satisfactory condition for all occupants. For buildings with occupants affected by a building-related illness, the lower limits of the standards of the American Society of Heating, Refrigerating, and Air Conditioning Engineers may not be sufficient.

Control of ventilation in residences is particularly difficult. Natural ventilation varies with weather conditions, construction, and occupant activities, and air exchange can be readily altered only if the house is equipped with a central heating and cooling system designed to control fresh air intake. Equipping a home with a heat exchanger, either a window unit or a central system, provides a modest increase in air volume exchange.

TABLE 16

COMMERCIALLY AVAILABLE SAMPLING EQUIPMENT FOR INDOOR AIR POLLUTANTS OTHER THAN PARTICULATES

Pollutant Sampler	Manufacturing Company	Sensitivity and Integrating Time	Approximate Cost
Radon: track etch detector	Terradex Corporation 460 N. Wiget Lane Walnut Creek, CA 94598 (415) 938-2545	1 to 3-month exposure 1 to 4 pCi/L	$20 to $60 depending on sensitivity desired
Radon: charcoal canister detector	RTCA 12 West Main Street Elmsford, NY 10523 (914) 347-5010	4 days 0.1 pCi/L	$35/canister includes shipment and analysis costs
Organic vapors	Industrial Scientific Corporation 355 Steubenville Pike Oakdale, PA 15071 (412)758-4353		
Organic vapors: hydrocarbon chemical reaction tubes	National Draeger Inc. P.O. Box 120 Pittsburgh, PA 15230 (412) 787-8383	100 to 3,000 ppm for 4 to 8 h	$3/tube, $900 for pump and accessories
Organic vapors: charcoal badges	3M Corporation Technical Service Department 3M Center St. Paul, MN 55144 (612) 733-1110	Depends on vapors and sampling times; minimum level, 10/mg	$10/badge, $50 to $300 analysis by GC or GC/MS
Formaldehyde: diffusion tube	Air Quality Research, Inc. 901 Grayson Street Berkeley, CA 94710 (415) 644-2097	5 to 7 days	$48 kit, includes 2 monitors analysis and report
Formaldehyde: pro-tek adsorption badge	E I. Dupont Company Applied Technical Division P.O. Box 110 Kennett Square, PA 19348 1 (800) 344-4900	1.6 to 64 ppm/h up to 7 days or 0.2 to 6.75 ppm/8 h TWA	$20/badge, $25 to $80 for analysis
Formaldehyde diffusion monitor	3M Corporation Technical Service Dept. Building 260-3-2 3M Center St. Paul, MN 55144 (612) 733-1110	0.1 ppm for 8 h	$37/monitor and analysis
NO_2: personal and alarm	MDA Scientific 405 Barclay Blvd Lincolnshire IL 60069 1 (800) 323-2000	2 to 3 ppm; 1/3 TLV electrochemical cell based 15 min to 8 h TWA	$800/dectector $100/output $2.075/ dosimeter, $1.045/ readout unit
NO_2: diffusion tubes	Environmental Sciences and Physiology Harvard School of Public Health 665 Huntington Avenue Boston, MA 02115 (617) 732-1000	500 ppb/h integrated	$10/tube, research only
NO_2: diffusion badge	Environmental Sciences and Physiology Harvard School of Public Health 665 Huntington Avenue Boston, MA 02115 (617) 732-1000	50 ppb/h	$15/badge, research only
CO: passive badge	Lab Safety Supply Co. P.O. Box 1368 Janesville, WI 53547 (608) 754-2345	50 ppm for 8 h produces color change	$3/holder, $12 75/10 indicating papers
CO: detector tube integrated	National Draeger Inc. P.O. Box 120 Pittsburgh, PA 15230 (412) 787-8383	2.5 ppm for 8 h	$255 pump and accessories, $3/tube
CO, detector tube grab	Sensidyne Inc. 12345 Sparkey Road Suite E Largo, FL 33543 (813) 530-3602	5 ppm/min	$130 pump, $2/tube

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Air Cleaning

Particles and gases can be cleansed from air with devices manufactured for use in office and residential environments. Devices to remove particles generally operate by mechanical filtration, electrostatic precipitation, or negative ion generation. Depending on the type of device, the efficiency of particle removal depends on particle sizes, filter design, electrostatic effects of the filter medium, and air-flow rate.

Air cleaning devices are frequently used in the home and office settings to control environmental tobacco smoke. The submicron-sized particles in tobacco smoke are not efficiently removed by conventional filters, although more costly high efficiency filters can clear these particles. Thus, most portable residential air cleaners are not satisfactory for tobacco smoke (407, 408). Their filters collect only the coarser particles of a few microns or larger in diameter, and the rated flow capacities of many units are too low to clean the full volume of a room. The most effective units have negative ion generators or high efficiency filters. The negative ions released by a negative ion generator attach to particles and increase particle removal through plateout onto surfaces and through coagulation.

Many of the small air-cleaning devices manufactured for residential use are also unsatisfactory for pollens and other indoor allergens (409). High efficiency filtration devices are more effective for removal, but their clinical utility has not been established (409, 410). Pollen exposure can be reduced by use of a conventional window air conditioner (411, 412). These devices can cool inside air without mixing in outside air (409, 412).

Gases can be removed from indoor air by chemical absorption of reactive substances or by physical adsorption onto surfaces. Activated charcoal filters, silica gel, activated alumina, and alumina oxide impregnated with potassium permanganate have been used for industrial air cleaning for years. More recently, hybrid air cleaners for residential use have included devices for removing gases. Removal efficiency approaching 25% for formaldehyde and 45% for NO_2 has been reported (408). However, the test situation in this report, a 2-h trial in a closed chamber, does not realistically simulate the circumstances of use in a home.

Remedial Action for Radon

The recognition that high levels of radon occur in some homes has led to the development and implementation of procedures for mitigation (376). Entry of radon into a home can be reduced by techniques that direct the radon away from the home, by sealing cracks and other portals of entry, by venting sump pumps, and by removing materials that are high in radium. Air treatment also reduces radon daughter concentrations as does increasing the air exchange rate.

TABLE 17

MONITORING EQUIPMENT FOR PARTICULATES* FOR INDOOR AIR QUALITY STUDIES

Instrument Method	Manufacturing Company	Flow Rate or Sensitivity	Approximate Cost
Integrated gravimetric; particles < 3.5 μm diameter	Cyclone separators with filter Several manufacturers cyclones, filters, and pumps	1.7 L/m	Pumps $200 to $700; filters $2; cyclones $20 to $100
Integrated gravimetric; particles between 10 and 3 μm and less than 3 μm diameters	National Bureau of Standards under EPA Contract USEPA Research Triangle Park, NC 27711 (919) 541-2350	6 L/m Separates using filters in series Batteries	Unknown
Integrated gravimetric; particles < 10 μm or < 2.5 μm diameter	Harvard Impactor Environmental Sciences Harvard School of Public Health 665 Huntington Avenue Boston, MA 02115 (617) 732-1000	4 L/m Mass flow controller for 14-day timer, double impactor for sharp cut; fixed location	$2,500
Instantaneous (2/10 s), TSP or RSP; 0.1 to 10 μ forward light-scattering	GCA-Mini-RAM (personal aerosol monitor) GCA Corporation 213 Burlington Road Bedford, MA 01730 (617) 275-5444		
Semiinstantaneous; RSP	Piezobalance (Model 3500) TSI Inc. P.O. Box 64394 St. Paul, MN 55164 (612) 483-0900	>10 μg/m³ 2-min average depending upon concentraton	$3,000 to $5,000
Continuous; RSP submicron light-scattering multisensor monitor	Handheld Aerosol Monitor (HAM) PPM Inc. 11428 Kingston Pike Knoxville, TN 37922 (615) 966-8796	>10 μg/m³ mass concentration, 1.5 L/s	$3,000 to $10,000

* Particles can be measured using a variety of techniques. Using cyclone or impactor separators, smaller size fractions can be collected on filters. Mass can also be measured using the optical properties of particles. For the most part, measuring particles requires equipment costing several hundred to a few thousand dollars. Equipment using filters require that they be preweighed and postweighed in a temperature- and humidity-controlled room.

Assessment of Indoor Air Quality

Continuous and integrated samplers are now available for many pollutants in indoor air. The continuous samplers are expensive devices that record real-time concentrations. The instruments for CO, NO_2, formaldehyde, CO_2, and other gases operate on electrochemical, chemoluminescent, or infrared absorbing principles. Costs range between $2,000 for a single gas detection system to more than $12,000 for a tunable wavelength multigas detector. Calibration gases and recording devices add to the costs of using continuous instruments.

Fortunately, less expensive samplers that integrate pollutant concentrations over time have been developed for many gases and particles (38, 39). We list some of these devices in tables 16 and 17, without implying our endorsement. Many of these devices operate by permeation or diffusion; for example, passive samplers are available for NO_2, radon, formaldehyde, and several other organic vapors. Other devices are more sophisticated and incorporate a pump to move air across a filter or vapor trap. With the exception of the colorimetric stain tubes available for industrial hygiene applications, most of these samplers require a laboratory for analysis.

Assessment of particle exposures may require special techniques. For some applications, particle mass alone may be sufficiently informative, but characterization of particle size, morphology, and

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chemical and elemental composition may also be necessary.

Conclusions

Research Recommendations

With the exception of airborne infection, the health effects of indoor air pollution received little attention until the early 1970s (413). The research performed subsequently has convincingly demonstrated the importance of indoor environments in determining personal exposures, but it has left unanswered many questions concerning health effects. We will address research needs related to methodology and to specific pollutants.

Methodology. In designing investigations of the health effects of indoor and outdoor pollutants, exposure assessment must be guided by the concept of total personal exposure (figure 1). The optimal approach for exposure assessment is measurement of each subject's personal exposure. For certain pollutants, such as NO_2 and CO, this approach is now feasible. For some pollutants, however, accurate and inexpensive devices are not available, and surrogate measures of exposure, such as source descriptions, are often used in the place of measurements. Studies of personal exposure have shown that misclassification of exposure is inevitably introduced by use of surrogate measures. Therefore, when an investigator relies on surrogate sources of exposure information, the extent of the resulting misclassification should be measured and considered in interpreting the study's results. For certain pollutants biological markers may quantify exposure.

In this review, we have described many studies limited by potential confounding and inadequate sample size. At the concentrations of pollutants generally found in indoor air in U.S. buildings, the anticipated health effects to be evaluated will often be subtle and of small magnitude. Investigations of such low-level effects should not be undertaken without assessment of sample size requirements. Consideration must also be given to misclassification of health outcomes and of exposure and to the implications of misclassification for sample size needs.

Epidemiologic investigations must provide accurate estimates of the low-level effects anticipated for many environmental pollutants. Apparent small effects may be introduced by uncontrolled confounding by environmental and host factors. Therefore, accurate measurement of potentially important covariates must be incorporated into the study design.

Involuntary Exposure to Tobacco Smoke. Research recommendations on involuntary smoking must consider the extensive data available on active smoking, which have long provided sufficient rationale for smoking prevention and cessation. In the face of incontrovertible evidence on active smoking, further research on involuntary smoking is warranted to describe more fully effects on infants and children, to characterize further nonmalignant effects on adults of exposure at home and at work, and to develop more precise risk estimates for lung cancer associated with involuntary smoking. It must be recognized that involuntary smoking affords an important research opportunity for describing exposure-response relationships for a potent and ubiquitous environmental pollutant. Furthermore, the results of research on involuntary smoking are needed to determine the magnitude and acceptability of risks incurred by nonsmokers.

Nitrogen Dioxide. Data from investigations of NO_2 exposure and respiratory illnesses indicate that the magnitude of the effect is likely to be small and less than that of involuntary exposure to tobacco smoke. However, because more than half of U.S. homes have gas cooking stoves and childhood respiratory illness is extremely common, even a small effect of NO_2 is of public health importance. In order to detect associations of the anticipated small magnitude, future investigations should employ direct measurements of exposure, rather than using surrogate variables. Infants and other potentially susceptible groups seem the most suitable populations for study.

Woodsmoke. Woodsmoke is a complex mixture of gases and particles that have a wide range of potential respiratory effects. The unconfirmed observations of Honicky and coworkers (241) that woodsmoke causes acute respiratory illnesses and symptoms in U.S. children require further study. Investigations in less developed countries suggest that domestic smoke exposure contributes to the development of chronic lung disease. This important hypothesis cannot be tested with sufficient sensitivity in most populations in the United States, but should be pursued in appropriate locales.

Formaldehyde. Although the irritant properties of formaldehyde are documented, evidence on health effects at concentrations found in residences and offices is inconclusive. Respiratory effects and neurobehavioral impairment have been associated with formaldehyde exposure, but many of the studies may have been biased by the approaches used for subject selection and data collection. These health outcomes should receive further investigation in populations selected without bias and with measured exposures. Appropriate control populations should be included in cross-sectional and cohort studies. Continued investigation of workers exposed to formaldehyde is needed to resolve the current controversy concerning carcinogenicity.

Radon and Radon Daughters. Radon daughters, like tobacco smoke, are an established cause of lung cancer. Research needs on environmental exposure relate to more precise quantitation of the risks of lung cancer. The requisite information includes population-based data on the distribution of exposure, risk estimates developed at lower levels of exposure than sustained by many of the mining groups evaluated to date, and improved understanding of factors modifying the risks of radon daughter exposure and of the temporal expression of radon-related lung cancer. Epidemiologic investigations of the association between domestic exposure and lung cancer may be informative, but methods for estimating exposures must be further developed.

Building-related Illness. Health hazard evaluations have documented the syndrome of building-related illness, but have not adequately defined its clinical dimensions and causes. Further health hazard evaluations of new outbreaks would be more informative if standardized methods were developed and adopted for assessment of exposures and health outcomes. However, more rigorous epidemiologic methods should also be applied to the problem of building-related illness. Both cross-sectional and longitudinal investigations may be informative if combined with a comprehensive environmental characterization.

Clinical Implications

Although much of the evidence on the health effects of indoor air pollution remains equivocal, some of the exposure-disease associations are established and clinically relevant. Involuntary smoking contributes to lower respiratory illnesses in infants, and mothers should be advised about this adverse effect and the possibility that their smoking will harm their child's developing lung. Active smokers should consider the lung cancer risk that their smoking imposes on nonsmokers.

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Carbon monoxide poisoning and hypersensitivity pneumonitis are well described clinical entities that may be overlooked. Indoor routes of exposure should also be considered in outbreaks of Legionnaires' disease, *Aspergillus*, and other infections. High radon and radon daughter levels should prompt mitigation.

The evidence is less compelling for other exposures, and we cannot provide firm guidance. For woodsmoke, the study reported by Honicky and coworkers (241) suggests that woodstoves may cause recurrent respiratory illness in children, but the findings have not been confirmed. The effects of formaldehyde exposure in residences, offices, and other environments also have not been well-characterized. Formaldehyde should be considered as a potential cause of vague respiratory and neuropsychologic symptoms and of asthma, but the diagnosis of formaldehyde-induced asthma should not be made without confirmation by inhalation challenge. Formaldehyde exposure may cause mucous membrane irritation in residents of mobile homes, new homes, and homes with potentially strong sources, such as new carpeting. The diagnosis of a building-related illness should be considered in persons with appropriate symptoms and employment in a sealed building. However, criteria for making this diagnosis in an individual patient have not been established.

Some exposures to indoor air pollutants are probably not associated with adverse effects that are clinically relevant. The epidemiologic studies indicate only minimal effects of NO_2 from gas stoves. Woodsmoke and involuntary exposure to tobacco smoke have not been associated with short-term effects in adults, but the relevant data are scant.

Health care providers can offer some practical suggestions to patients who ask about air cleaning. Only a few of the commercially available devices effectively remove tobacco smoke and pollens (405, 406). However, closing windows and using a window air conditioner reduces pollen counts (407, 409, 410). Some exposures can be readily controlled by removal of the source, such as tobacco smoking and unvented space heaters, or by proper venting and use of exhaust fans, such as with gas stoves. Merely opening a window to increase ventilation may be effective.

Health care providers may also be viewed as expert on the health effects of indoor air pollution, as on other health topics. In recent years, the communications media have regularly transmitted the results of studies and reports on indoor air pollution. Patients may turn to their health care providers for information on radon, involuntary smoking, gas stoves, and other prevalent exposures. This review provides some information for answering these questions.

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Addendum

During 1987, several new sources of information on indoor air pollution and health have been published. The 4th International Conference on Indoor Air Quality and Climate was held in August 1987. The proceedings were published by the Institute for Water, Soil and Air Hygiene in Berlin (mailing address: Institut für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes, Corrensplatz 1, D-1000 Berlin 33). The U.S. Environmental Protection Agency report "EPA Indoor Air Quality Implementation Plan" and its appendices provide a comprehensive review. Two new reports on environmental radon are available: "Lung Cancer Risk from Indoor Exposure to Radon Daughters," Publication 50 of The International Commission on Radiological Protection, and the report of the Biological Effects of Ionizing Radiation (BEIR) IV Alpha Committee of the National Academy of Sciences.

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